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(54) Process and equipment for study of chemical reactions in miniaturized reactors operated in parallel

(67) The subject of the invention is a process for study of chemical reactions, in which the reactions are run in parallel in reactors, characterized in that the reactions are carried out in miniaturized reactors and the reaction mixture or the reaction products are analyzed during the reaction period. A further subject of the invention is equipment with reactors having input and output lines, characterized in that the reactors are miniaturized, with volumes in the range of 0.001 cm^3 to 1 cm^3.

The major advantages are that many reactions can be carried out under practically identical conditions with relatively small amounts of substance and samples, economically and reproducibly, and that the reactions can be examined simultaneously by spectroscopy. Thus it offers the possibility of using the potential for industrial catalyst screening that have been discussed with respect to combinatorial chemistry. Reaction optimization can be carried out in parallel by choosing identical samples and various other reaction conditions.

Description

The invention concerns a process for study of chemical reactions, in which the reactions are carried out in parallel in reactors. The invention further concerns equipment particularly for carrying out this process, which equipment comprises multiple reactors operated in parallel, with input and output lines.

Processes and equipment of the type indicated are known. They are used in, among other things, search for catalysts for heterogeneous or homogeneous catalysis of industrial chemical processes. Very recently, though, new techniques have made it possible to produce larger numbers of substances which could be potential catalysts for many chemical processes (P. G. Schultz et al., Science 1995, 1738). It is hardly possible any longer to investigate this multitude of potential catalysts with the usual serial screening procedures, as these screening procedures are limited in their throughput and analytical resolution. Often completely inadequate integral effects such as heating the catalyst, etc., are used, without direct analysis of the product mixture or effectiveness analyses. Furthermore, optimization of the conditions for catalyst activation and process control place special requirements on quantitative analytical procedures and on the reproducibility of the reaction conditions.

Thus the invention is based on the objective of developing an economical process, or economical equipment, by which one can investigate many chemical reactions in a short time, and can get reproducible qualitative and quantitative data on the compositions of the various reaction mixtures and reaction products.

This objective has been attained by a process of the type stated initially, characterized by the fact that the reactions are carried out in miniaturized reactors and that the reaction mixture or the reaction products are analyzed during the reaction time.

The objective has also been attained by equipment of the type stated, characterized by the fact that the reactors are miniaturized, with volumes in the range of 0.001 cm^3 to 1 cm^3.

Therefore the subject of the invention is a process for studying chemical reactions, characterized by the fact that the reactions are carried out in miniaturized reactors and the reaction mixture or the reaction products are analyzed during the reaction time.

Another subject of the invention is equipment particularly for carrying out this process, such that the equipment comprises multiple reactors operated in parallel, with input and output lines, characterized by the fact that the reactors are miniaturized, with volumes in the range of 0.001 cm^3 to 1 cm^3.

Particular embodiments or forms of the invention appear in the individual subclaims. One or more of the individual characteristics mentioned in the claims can present the solution according to the invention and the characteristics may be combined as desired within the claim categories.

One particular embodiment of the process according to the invention is characterized by the fact that that the reactants are fed continuously to the reactors and the reaction products are removed continuously from the reactors. However, batch processing is also possible.

Another particular embodiment is characterized in that at least some of the reactants used are isotopically labeled, preferably with deuterium (^2H) or heavy oxygen (^{18}O) or heavy carbon (^{13}C) or mixtures of them. They cause characteristic spectral shifts in rotational/vibrational spectra. That, along with reaction path marking by variations of the final product mixtures, can yield interesting new reactions or reaction products, and systematically contrasts smaller amounts of byproducts.

Different reactant mixtures can also be fed to individual reactors or to reactors combined in groups, so that potential synergism can be recognized or discovered using methods of combinatorial chemistry. The reactant, reaction, or product mixtures can be analyzed for the types and amounts of the substances contained by spectrometric analysis, preferably by infrared (IR) spectrometry, and especially preferably by Fourier IR spectrometry, at any times during the course of the reaction. Other spectrometric methods such as laser or UV spectrometry are also suitable for the investigation. The process can be run at different temperatures and pressures, at temperatures in the range of – 50 °C to 600 °C, preferably from room temperature to 500 °C, or at various pressures, at absolute pressures of 10^{-3} to 10^3 bar, preferably from 10^{-2} to 200 bar. The data obtained can be transferred for comprehensive parametric and data analysis.

The invention is further characterized by the fact that the reactions can be carried out in the presence of a catalyst, and that it is possible to screen the catalytic activity (i. e., determine the product) and selectivity (distribution of the main products) of catalyst amounts less than 10 mg, preferably less than 1 mg in one reactor.

In one special embodiment of the equipment according to the invention, multiple separate miniaturized reactors can be arranged in a block. The volumes of these reactors can be in the range of 0.001 cm^3 to 1 cm^3, preferably 0.01 cm^3 to 0.5 cm^3, and especially preferably from 0.05 cm^3 to 0.2 cm^3. In another preferred embodiment of the equipment according to the invention the reactors are arranged in a square or rectangular pattern in a metal block, which can be rectangular or cubical. The metal block can have heating or cooling elements and can have a temperature-control sensor near each reactor. That allows controlled and reproducible temperature management. For example, a definite temperature gradient can be established across the metal block. The reactors are advantageously arranged in a plane parallel to one surface of the rectangle. The input and output lines for the individual reactors are advantageously at least partially perpendicular to that plane. They can be designed as holes through the metal block. The reactors can be designed as holes. The number of reactors in a block can be greater than 20, preferably greater than 40, especially preferably greater than 100, and very especially preferably

greater than 200. With these reactors, small quantities of potential catalysts (also called samples in the following) can be brought simultaneously into contact or reaction with reactants or reactant mixtures in liquid or gaseous form. The system according to the invention can be automated. In particular, loading the catalysts into the reactors can be done automatically, preferably by a laboratory robot or a pipettor.

In another special embodiment, the miniaturized reactors are made as 4 mm holes in the metal block, arranged so that various reactant and inert gases can be passed through them from 2.5 mm capillary holes. Then the gases go to a spacer, preferably a distance plate[1], which is placed on the metal block and into which the holes in the metal block continue. The arrangement of metal block and spacer has an open cuvette hole in which the gases can be analyzed spectrometrically. For that purpose, the hole is closed at both ends with a transparent window. If one wishes to use infrared spectrometry for analysis, it is preferable to use windows of 1-1-1 silicon, NaCl, KBr, Ge, ZnSe or KSR5. For the analysis, one uses a collimated analytical beam. This is an infrared beam for IR spectrometry. It is preferably coupled out of an interferometer without mirrors, and is directed through a space flushed with dry gas, through the cuvette hole, and onto a detector behind it. The cuvette hole can, for example, be 5 mm thick. By selecting a spacer of suitable thickness, the length of the cuvette hole can be chosen from a few cm (1-10) and several tens of cm (10-50), depending on the nature and conditions of the reaction. To record the spectra, the analysis beam can be directed in succession through all the cuvette holes by a directing system. However, it is also possible to use multiple beams or multiple analyzers so that it is possible to record spectra from multiple reactors simultaneously. It is also possible to equip the block holding the reactors with transport units, such as stepping motors, so that the block can be moved so that all the cuvette holes are brought successively to the spectrometer beam path. The usual corrosion-resistant metallic materials used by those skilled in the art are preferred as materials for the block and spacer, especially aluminum or steel, preferably stainless and/or acid and/or high-temperature resistant.

Another embodiment of the equipment according to the invention, particularly suitable for homogeneous catalysis, is characterized by the fact that in at least one reactor having a volume preferably less than 200 µl the spectrometric contact with the reaction mixture is provided by an ATR (Attenuated Total Reflection) crystal (preferably a pointed cone, preferably of ZnSe or KSR5 or diamond). This allows various solvents and reaction conditions and pressures up to 200 bar. In this case, the analytical beam is focused onto the ATR crystal.

The advantages of the process and equipment according to the invention are essentially that many reactions can be carried out rapidly, economically, and reproducibly under

[1] German: *Distanzplatte* = distance plate. Overly literal, but the description is not clear enough to allow much alternative; possibly a 'stand-off' plate.

practically identical conditions and with relatively small quantities of materials and samples, and that they can be examined simultaneously by spectrometry. Thus they offer the possibility of applying the potentials discussed in relation with combinatorial chemistry (K. Burgess et al., Ang. Chem. 1996, 108, 2, 192, made part of the application by reference) to industrial catalyst screening. By selection of identical samples and varying other reaction conditions such as temperature, pressure, and reactant composition one can carry out parallel reaction optimization.

To analyze the data obtained, it is advantageous to establish a data matrix such that all the selectable and documentable reaction conditions (reactant partial pressures, reactant compositions, temperature, flow or flow rate, total pressure, sample composition, sampling grid parameters and all the spectral reference points) are presented as columns of the matrix according to the reaction conditions, i. e., by reactor. This matrix can be subjected to factor analysis (E. R. Malinowski et al., Factor Analysis in Chemistry, Wiley, New York, 1980, made part of the application by reference) by calculating the covariance matrix, the eigenvalues, the abstract eigenvectors, the loadings and the coefficients of multidimensional regression, preferably producing files. One can also select (pre)normalization of the data by the mean "0" and standard deviations "1", so that baseline or absolute quantity effects can be avoided. That allows prediction of various quantities and sets of calibration data (such as quantitative CO_2 proportions at various temperatures), determination of the dependence of parameters in spectral regions for optimizing the analysis, generation of various distance matrices from the initial data

(e. g., similarity of catalysts with respect to the selected quantities and properties) and direct feedback of catalyst composition to a synthetic laboratory robot which mixes a set of new catalysts, and synthesizes them "independently" by sintering or calcining on a robotic line.

One embodiment of the process according to the invention and one form of the equipment according to the invention is explained in more detail by means of Figures 1 and 2, without the intent to limit the invention in any way.

Figure 1 shows a schematic representation of the equipment according to the invention in the beam path of a spectrometric analyzer.

Figure 2 shows an individual reactor 2 from the equipment according to the invention, 1, in a section seen from the side.

An equipment 1 for study of chemical reactions comprises essentially a block-like arrangement 3 of miniaturized reactors 2 in a rectangular metal block 4 which has a front side 6 and a back side 7. The reactors 2 are inserted as holes into the front side 6 of the rectangular metal block 4 and are arranged in a rectangular pattern. They are connected with holes 5 for feeding in the reactants. Catalysts 8 are placed in the reactors 2. A distance plate 9 is placed on the front side 6 as a spacer. The reactors 2 continue as holes

into the distance plate. From those, other holes 10, which carry off the reaction products, lead to a cuvette hole 11. A distance plate 12 acting as another spacer is placed on the back side. The cuvette hole continues through the metal block 4 and through the distance plate 12. It is closed at the free surface of the distance plate with transparent windows 13 and serves simultaneously to lead off the reaction products and to provide a space for spectrometric analysis of them with an IR beam 14. The reaction products from the reactor 2 are led through the holes 10, 11 as shown by the arrows. From the end of the cuvette hole 11 they are led through holes 15 to the distance plate 12. Heating elements 17 and thermocouples 18 are placed in the metal block 4 near the reactors 2. The block-like arrangement 3 can be moved in both the spatial directions perpendicular to the IR beam by stepping motors 16. Thus any cuvette hole assigned to one of the reactors 2 can be moved into the IR beam. The IR beam is analyzed by recording the interferogram with an interferometer 20 and a detector 19, which are placed near the transparent window 13.

Claims

1. Process for study of chemical reactions, in which the reactions are carried out in parallel in reactors, characterized in that the reactions are carried out in miniaturized reactors and the reaction mixture or the reaction products are analyzed during the reaction time.

2. Process according to Claim 1, characterized in that reactants are fed continuously to the reactors and the products are removed continuously from the reactors.

3. Process according to Claim 1 or Claim 2, characterized in that the reactions are carried out at different temperatures, preferably at temperatures in the range of room temperature up to and including 600 °C or at different pressures, preferably at absolute pressures of 10^{-3} to 10^{3} bar, especially preferably from 10^{-2} to 200 bar.

4. Process according to one or more of Claims 1 to 3, characterized in that the reactions are carried out in the presence of a catalyst.

5. Process according to Claim 4, characterized in that less than 10 mg and preferably less than 1 mg of catalyst is used per reactor.

6. Process according to one or more of Claims 1 to 5, characterized in that the reaction mixture or the reaction products are analyzed spectrometrically for the nature and amount of the components, preferably by IR spectrometry.

7. Process according to one or more of Claims 1 to 6, characterized in that the reactions are carried out in more than 20, preferably more than 40, and especially preferably in more than 100 reactors.

8. Process according to one or more of Claims 1 to 6, characterized in that reactions of homogeneous or heterogeneous catalysts are investigated with liquid or gaseous reactants or products.

9. Process according to Claim 6, characterized in that the spectrometric analyses are done simultaneously for all reactors by using a corresponding number of analyzers, or that the spectrometric analyses are done in succession at the reactors by directing an analytical beam successively, by means of a directing system, onto the individual reactors, or by bringing the reactors successively into the analytical beam by means of a moving arrangement.

10. Process according to one or more of Claims 1 to 9, characterized in that one uses reactants, at least some of which are labeled with isotopes, preferably with deuterium or heavy oxygen or heavy carbon.

11. Process according to one or more of Claims 1 to 10, characterized in that different reactant mixtures are fed to individual reactors or groups of reactors.

12. Equipment, particularly for conduct of the process according to Claim 1, with the equipment having multiple reactors connected in parallel, provided with input and output lines, characterized in that the reactors are miniaturized and have volumes in the range of 0.001 cm^3 to 1 cm^3.

13. Equipment according to Claim 12, characterized in that the reactors are arranges in the form of blocks, preferably square or rectangular.

14. Equipment according to Claim 12 or Claim 13, characterized in that the input or output lines or the reactors are at least partially transparent to the analytical beam, preferably for infrared, laser, or UV light.

15. Equipment according to one or more of Claims 12 to 14, characterized in that the reactors are arranged in a rectangular metal block provided with heating elements and/or temperature sensors.

16. Equipment according to one or more of Claims 12 to 15, characterized in that the equipment is provided with means for movement, preferably with stepping motors.

17. Equipment according to one or more of Claims 12 to 16, characterized in that the equipment has more than 20, preferably more than 40, especially preferably more than 100, and very especially preferably more than 200 reactors.

18. Equipment according to one or more of Claims 12 to 17, characterized in that at least one reactor is provided with an ATR crystal which allows spectrometric contact with the reaction mixture.

19. Equipment according to Claim 15, characterized in that the reactors are arranged in a plane parallel to one surface of the metal block; that at least segments of the input or output lines are perpendicular to that plant; that a spacer having holes through which the reactors or the output lines can be extended is placed on the surface; that the metal block and the spacer have cuvette holes; and that the spacer has windows transparent to the analytical beam which close off the cuvette holes from the environment.

20. Equipment according to one or more of the Claims 12 to 19, characterized in that the reactors contain catalysts, preferably with weights less than 10 mg per reactor, and especially preferably with weights less than 1 mg per reactor.

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accompanied by 2 pages of drawings
